Themed Issue: Drug Addiction - From Basic Research to Therapies
Guest Editors - Rao Rapaka and Wolfgang Sadée

Drug Discovery From Natural Sources

Submitted: January 24, 2006; Accepted: February 19, 2006; Published: April 14, 2006

Young-Won Chin,[1] Marcy J. Balunas,[1,2] Hee Byung Chai,[1] and A. Douglas Kinghorn[1]

[1]Division of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, The Ohio State University, Columbus, OH 43210
[2]Program for Collaborative Research in the Pharmaceutical Sciences, Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, University of Illinois at Chicago, Chicago, IL 60612

ABSTRACT

Organic compounds from terrestrial and marine organisms have extensive past and present use in the treatment of many diseases and serve as compounds of interest both in their natural form and as templates for synthetic modification. Over 20 new drugs launched on the market between 2000 and 2005, originating from terrestrial plants, terrestrial microorganisms, marine organisms, and terrestrial vertebrates and invertebrates, are described. These approved substances, representative of very wide chemical diversity, together with several other natural products or their analogs undergoing clinical trials, continue to demonstrate the importance of compounds from natural sources in modern drug discovery efforts.

KEYWORDS: natural products, drug discovery, terrestrial plants, terrestrial microorganisms, marine organisms, terrestrial vertebrates, terrestrial invertebrates, chemical diversity

INTRODUCTION

For thousands of years, natural products have played an important role throughout the world in treating and preventing human diseases. Natural product medicines have come from various source materials including terrestrial plants, terrestrial microorganisms, marine organisms, and terrestrial vertebrates and invertebrates.[1] The importance of natural products in modern medicine has been discussed in recent reviews and reports.[1-6] The value of natural products in this regard can be assessed using 3 criteria: (1) the rate of introduction of new chemical entities of wide structural diversity, including serving as templates for semisynthetic and total synthetic modification, (2) the number of diseases treated or prevented by these substances, and (3) their frequency of use in the treatment of disease.

An analysis of the origin of the drugs developed between 1981 and 2002 showed that natural products or natural product-derived drugs comprised 28% of all new chemical entities (NCEs) launched onto the market.[2] In addition, 24% of these NCEs were synthetic or natural mimic compounds, based on the study of pharmacophores related to natural products.[1] This combined percentage (52% of all NCEs) suggests that natural products are important sources for new drugs and are also good lead compounds suitable for further modification during drug development. The large proportion of natural products in drug discovery has stemmed from the diverse structures and the intricate carbon skeletons of natural products. Since secondary metabolites from natural sources have been elaborated within living systems, they are often perceived as showing more "drug-likeness and biological friendliness than totally synthetic molecules,"[3] making them good candidates for further drug development.[5,7]

Scrutiny of medical indications by source of compounds has demonstrated that natural products and related drugs are used to treat 87% of all categorized human diseases (48/55), including as antibacterial, anticancer, anticoagulant, antiparasitic, and immunosuppressant agents, among others.[2] There was no introduction of any natural products or related drugs for 7 drug categories (anesthetic, antianginal, antihistamine, anxiolytic, chelator and antidote, diuretic, and hypnotic) during 1981 to 2002.[2] In the case of antibacterial agents, natural products have made significant contributions as either direct treatments or templates for synthetic modification. Of the 90 drugs of that type that became commercially available in the United States or were approved worldwide from 1982 to 2002, ~79% can be traced to a natural product origin.[2]

Frequency of use of natural products in the treatment and/or prevention of disease can be measured by the number and/or economic value of prescriptions, from which the extent of preference and/or effectiveness of drugs can be estimated indirectly. According to a study by Grifo and colleagues,[8] 84 of a representative 150 prescription drugs in the United States fell into the category of natural products and related drugs. They were prescribed predominantly as anti-allergy/pulmonary/respiratory agents, analgesics, cardiovascular drugs, and for infectious diseases. Another study found that natural products or related substances accounted for 40%, 24%, and 26%, respectively, of the top 35 worldwide ethical drug sales from 2000, 2001, and 2002.[9] Of these natural

Corresponding Author: A. Douglas Kinghorn, Division of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, The Ohio State University, Columbus, OH 43210. Tel: (614) 247-8094; Fax: (614) 247-8642; E-mail: kinghorn.4@osu.edu

product-based drugs, paclitaxel (ranked at 25 in 2000), a plant-derived anticancer drug, had sales of $1.6 billion in 2000.[10,11] The sales of 2 categories of plant-derived cancer chemotherapeutic agents were responsible for approximately one third of the total anticancer drug sales worldwide, or just under $3 billion dollars in 2002; namely, the taxanes, paclitaxel and docetaxel, and the camptothecin derivatives, irinotecan and topotecan.[10,11]

This short review covers new drugs derived from natural sources launched in the 6-year period from 2000 to 2005, and drug candidates from natural sources in clinical trials during the same time period arranged according to their origin (terrestrial plants, terrestrial microorganisms, marine organisms, and other natural sources). For drug candidates in clinical trials,[12] only examples of new chemical templates of potential cancer chemotherapeutic drugs will be mentioned.

Drug Discovery From Terrestrial Plants

Terrestrial plants, especially higher plants, have a long history of use in the treatment of human diseases. Several well-known species, including licorice (*Glycyrrhiza glabra*), myrrh (*Commiphora* species), and poppy capsule latex (*Papaver somniferum*), were referred to by the first known written record on clay tablets from Mesopotamia in 2600 BC, and these plants are still in use today for the treatment of various diseases as ingredients of official drugs or herbal preparations used in systems of traditional medicine.[1] Furthermore, morphine, codeine, noscapine (narcotine), and papaverine isolated from *P. somniferum* were developed as single chemical drugs and are still clinically used. Hemisuccinate carbenoxolone sodium, a semi-synthetic derivative of glycyrrhetic acid found in licorice, is prescribed for the treatment of gastric and duodenal ulcers in various countries.[13]

Historical experiences with plants as therapeutic tools have helped to introduce single chemical entities in modern medicine. Plants, especially those with ethnopharmacological uses, have been the primary sources of medicines for early drug discovery. In fact, a recent analysis by Fabricant and Farnsworth showed that the uses of 80% of 122 plant-derived drugs were related to their original ethnopharmacological purposes.[14] Current drug discovery from terrestrial plants has mainly relied on bioactivity-guided isolation methods, which, for example, have led to discoveries of the important anticancer agents, paclitaxel from *Taxus brevifolia* and camptothecin from *Camptotheca acuminata*.[15] Other NCEs discovered or modified from terrestrial plants between 2000–2005 are summarized below (Figure 1).[12]

Approved Drugs

Apomorphine hydrochloride (**1**, Apokyn, Bertek, 2004), a short-acting dopamine D_1 and D_2 receptor agonist, is a potent dopamine receptor agonist used to treat Parkinson's disease, a chronic neurodegenerative disease caused by the loss of pigmented mesostriatal dopaminergic neurons linking the substantia nigra (pars compacta) to the neostriatum (caudate nucleus and putamen). Apomorphine is a derivative of morphine isolated from poppy (*Papaver somniferum*). Subcutaneous apomorphine is currently used for the management of sudden, unexpected and refractory levodopa-induced off states in fluctuating Parkinson's disease.[16]

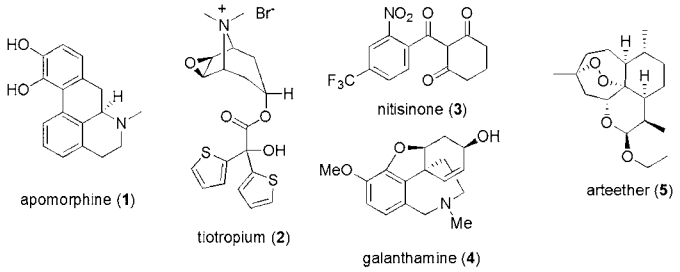

Figure 1. New drugs from terrestrial plants (2000 to 2005).

Tiotropium bromide (**2**, Spiriva Handihaler, Boehringer Ingelheim, 2004) has been approved by the United States Food and Drug Administration (FDA) for the treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD). Tiotropium, a derivative of atropine from *Atropa belladonna* (Solanaceae) and related tropane alkaloids from other solanaceous plants, is a potent reversible nonselective inhibitor of muscarinic receptors. Tiotropium is structurally analogous to ipratropium, a commonly prescribed drug for COPD, but has shown longer-lasting effects.[17]

Nitisinone (**3**, Orfadin, Swedish Orphan, 2002) is a derivative of leptospermone, an important new class of herbicides from the bottlebrush plant (*Callistemon citrinus*), and exerts an inhibitory effect for *p*-hydroxyphenylpyruvate dioxygenase (HPPD) involved in plastoquinone synthesis.[18] This drug has been used successfully as a treatment of hereditary tyrosinaemia type 1 (HT-1), a severe inherited disease of humans caused by a deficiency of fumaryl acetoacetate hydrolase (FAH), leading to accumulation of fumaryl and maleyl acetoacetate, and progressive liver and kidney damage.[19]

Galantamine hydrobromide (**4**, Reminyl, Janssen, 2001) is an Amaryllidaceae alkaloid obtained from *Galanthus nivalis* that has been used traditionally in Bulgaria and Turkey for neurological conditions,[20,21] and was launched onto the market as a selective acetylcholinesterase inhibitor for Alzheimer's disease treatment, slowing the process of neurological degeneration by inhibiting acetylcholinesterase as well as binding to and modulating the nicotinic acetylcholine receptor.[5]

Arteether (**5**, Artecef, Artecef BV, 2000), an antimalarial agent, has been developed from artemisinin, a sesquiterpene lactone isolated from *Artemisia annua* (Asteraceae), a plant

used in traditional Chinese medicine as a remedy for chills and fevers. Other derivatives of artemisinin are in various stages of clinical development as antimalarial drugs in Europe.[5,22]

Examples of Plant-derived Compounds Currently in Clinical Trials

From terrestrial plant-derived secondary metabolites, several new chemical entities (Figure 2) are undergoing clinical trials including four that are derivatives of known anticancer drugs (camptothecin, paclitaxel, epipodophyllotoxin, and vinblastine).[12] In addition, combretastatin A4, isolated from the South African medicinal tree, *Combretum caffrum* (Combretaceae), was derivatized to combretastatin A4 phosphate (**6**) and AVE-8062 (**7**).[23,24] These analogs bind to tubulin leading to morphological changes and then disrupt tumor vasculature, and are in phase II trials.[25,26] Homoharringtonine (**8**), a cephalotaxus alkaloid from the tree, *Cephalotaxus harringtonia* found in mainland China,[27] is an inhibitor of protein synthesis and is reported to have activity against hematologic malignancies.[28] Ingenol 3-*O*-angelate (**9**), an analog of the polyhydroxy diterpenoid, ingenol, which was originally obtained from *Euphorbia peplus* (known as "petty spurge" in England or "radium weed" in Australia), is a potential topical chemotherapeutic agent for skin cancer and exhibits its action through activation of protein kinase C.[29,30] Phenoxodiol (**10**), a synthetic analog of daidzein, a well known isoflavone from soybean (*Glycine max*), is being developed as a therapy for cervical, ovarian, prostate, renal, and vaginal cancers, and induces apoptosis through inhibition of anti-apoptotic proteins including XIAP and FLIP.[31] Phenoxodiol is currently undergoing clinical studies in the United States and Australia.[32] Protopanaxadiol (**11**), a derivative of a triterpene aglycone of several saponins from ginseng (*Panax ginseng*), exhibits its apoptotic effects on cancer cells through various signaling pathways, and is also reported to be cytotoxic against multidrug resistant tumors.[33,34] Triptolide, a diterpene triepoxide, was isolated from *Tripterygium wilfordii*, and has been used for autoimmune and inflammatory diseases in the People's Republic of China.[35] PG490–88 (**12**, 14-succinyl triptolide sodium salt), a semisynthetic analog of triptolide, exerts antiproliferative and proapoptotic activities on primary human prostatic epithelial cells as well as tumor regression of colon and lung xenografts.[36]

Drug Discovery From Terrestrial Microorganisms

Until the development of penicillin in the early 1940s, most natural product-derived drugs were obtained from terrestrial plants. The success of penicillin in treating infection led to an expansion in the area of drug discovery from microorganisms. Terrestrial microorganisms are a plentiful source of structurally diverse bioactive substances, and have provided important contributions to the discovery of antibacterial agents including penicillins, cephalosporins, aminoglycosides, tetracyclines, and polyketides.[13] Current therapeutic applications of metabolites from microorganisms have expanded into immunosuppressive agents (eg, cyclosporins and rapamycin), cholesterol-lowering agents (eg, lovastatin and mevastatin), antihelmintic agents (eg, ivermectin), an antidiabetic agent (acarbose), and anticancer agents (eg, pentostatin, peplomycin, and epirubicin).[2,12,37] Recently approved drugs derived from terrestrial microorganisms are shown in Figures 3, 4, and 5.

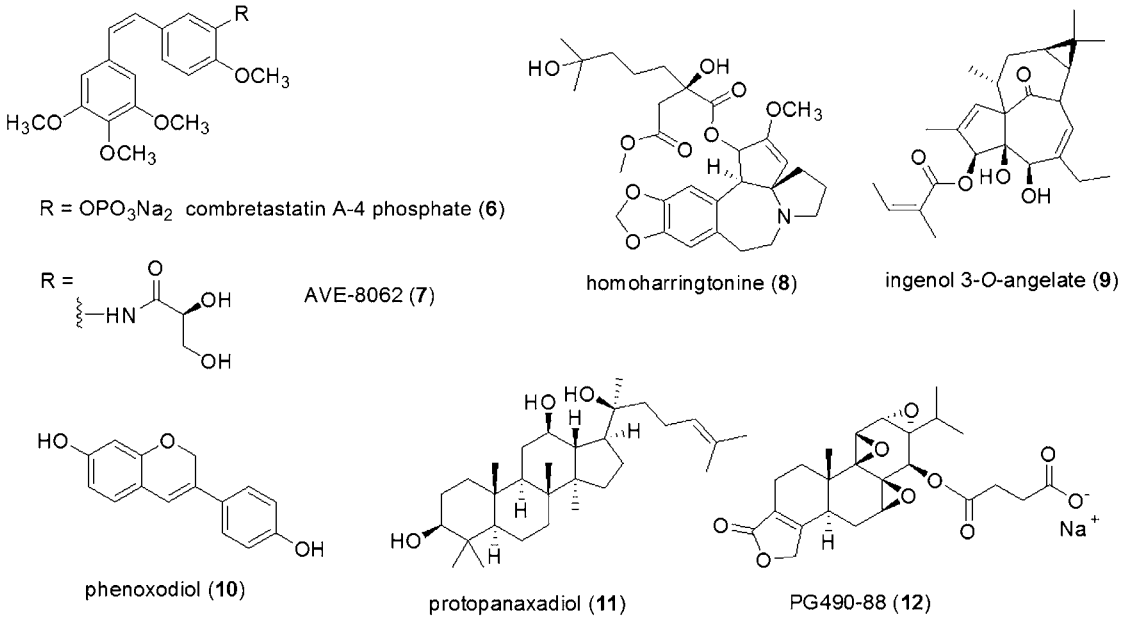

Figure 2. Plant-derived drug candidates.

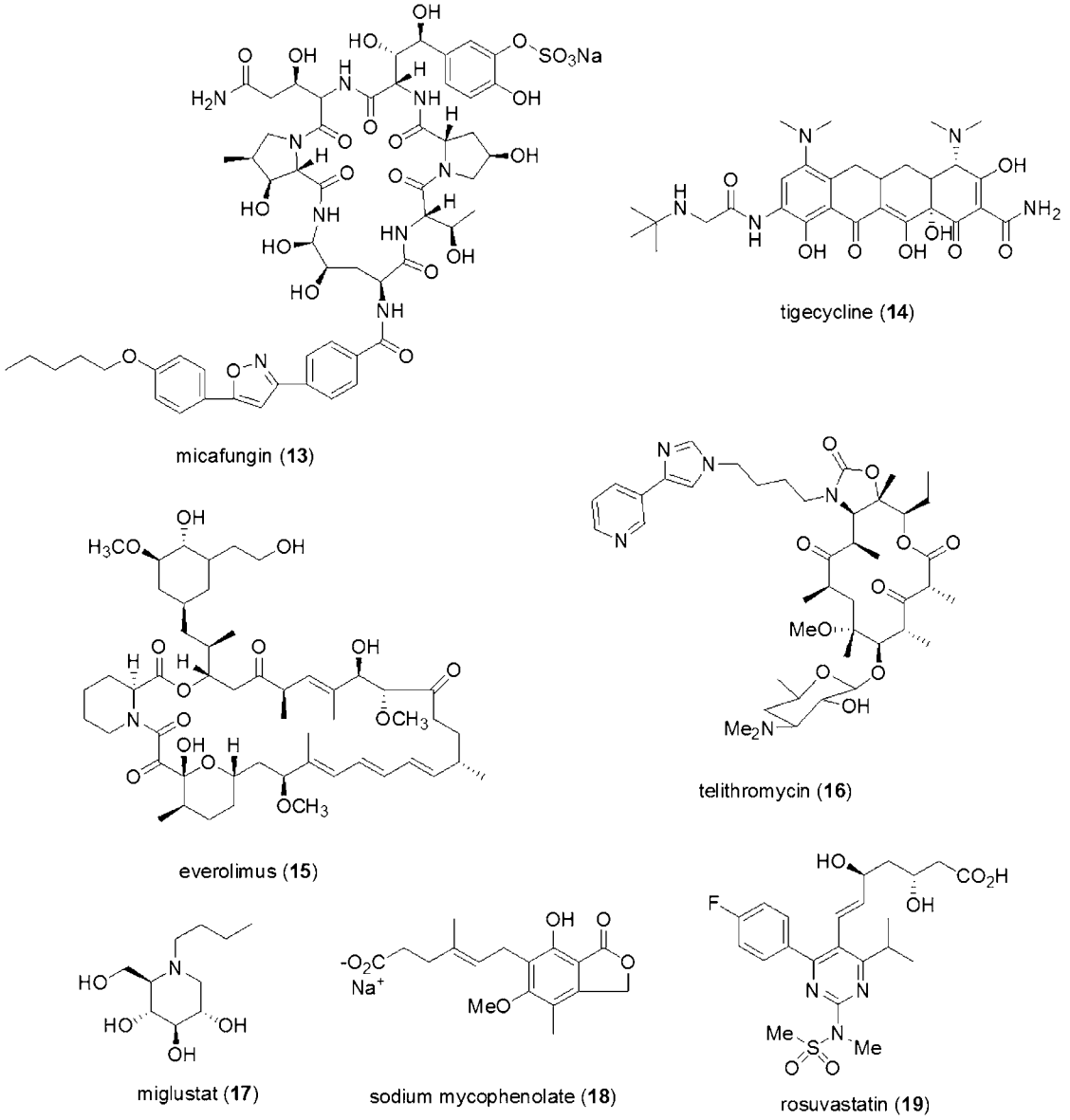

Figure 3. New drugs from terrestrial microorganisms (2000 to 2005).

Approved Drugs

Micafungin sodium (**13**, Mycamine, Fujisawa, 2005) is an antifungal agent of the echinocandin type obtained from the culture broth of the fungus *Coleophoma empetri*, and inhibits β-(1,3)-D-glucan synthase of fungi.[38,39] Micafungin exhibited good antifungal activity against a broad range of *Candida* species, including azole-resistant strains, and *Aspergillus* species, during in vitro and animal studies.[38]

Tigecycline (**14**, Tygacil, Wyeth, 2005) is the 9-*tert*-butyl-glycylamido derivative of minocycline, which is a semi-synthetic product of chlortetracycline isolated from *Streptomyces aureofaciens*. Tigecycline exhibited antibacterial activity typical of other tetracyclines, but with more potent activity against tetracycline-resistant organisms. Tigecycline is only utilized in an injectable formulation for clinical use, unlike currently marketed tetracyclines that are available in oral dosage forms.[40]

Everolimus (**15**, Certican, Norvatis, 2004) is an orally active 40-*O*-(2-hydroxyethyl) derivative of rapamycin, originally produced from *Streptomyces hygroscopicus*. Everolimus exhibits its immunosuppressive effect by blocking growth factor (interleukin (IL)-2 and IL-15) mediated proliferation of hematopoietic (T cells and B cells), and non-hematopoietic (vascular smooth muscle cells) cells through inhibiting p70 S6 kinase, leading to arrest of the cell cycle at the G_1/S phase.[41]

Telithromycin (**16**, Ketek, Aventis, 2004) is a semi-synthetic derivative of the 14-membered macrolide, erythromycin A, isolated from *Saccharopolyspora erythraea*, and retains the macrolactone ring as well as a D-desosamine sugar moiety. It inhibits protein synthesis by interacting with the

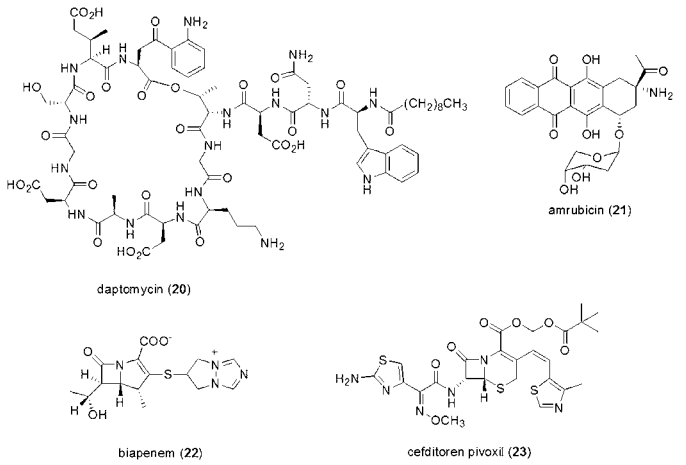

Figure 4. New drugs from terrestrial microorganisms (2000 to 2005).

peptidyltransferase site of the bacterial 50S ribosomal subunit, and exhibits antibacterial effect on respiratory tract pathogens resistant to other macrolides.[42]

Miglustat (**17**, Zavesca, Actelion, 2003) has been approved for patients unable to receive enzyme replacement therapy as a therapeutic drug for type I Gaucher disease. Miglustat, an analog of nojirimycin isolated from the broth filtrate of *Streptomyces lavendulae*, reversibly inhibits glucosylceramide synthase, a ceramide-specific glucosyltransferase that catalyzes the formation of glucocerebroside, and thereby decreases tissue storage of glucosylceramide. Gaucher disease is a progressive lysosomal storage disorder associated with pathological accumulation of glucosylceramide in cells of the monocyte/macrophage lineage. Enzyme replacement therapy using human placenta-derived alglucerase (Ceredase) has been available for type I Gaucher disease since 1991.[43,44]

Mycophenolate sodium (**18**, Myfortic, Norvatis, 2003) is a selective, noncompetitive, reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), the rate-limiting enzyme in the de novo pathway of guanosine nucleotide synthesis. Thus, mycophenolic acid, originally purified from *Penicillium brevicompactum*, has a selective antiproliferative effect on lymphocytes that rely on the de novo synthesis of purine and is used for the prophylaxis of organ rejection in patients receiving allogeneic renal transplants treated with ciclosporin (cyclosporin A) and corticosteroids.[45,46]

Rosuvastatin calcium (**19**, Crestor, AstraZeneca, 2003), an inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase and a derivative of mevastatin isolated from *Penicillium citrinum* and *P. brevicompactum*, is an effective lipid-lowering agent approved internationally (in most of Europe, the United States, and Canada) for the management of dyslipidemias.[47] Like other available HMG-CoA reductase inhibitors (atrovastatin, fluvastatin, lovastatin, pravastatin, and simvastatin), rosuvastatin competitively inhibits the rate-limiting step in the formation of endogenous cholesterol by HMG-CoA reductase. Consequently, hepatic intracellular stores of cholesterol are reduced, which results in reduced serum levels of low-density lipoprotein-cholesterol (LDL-C) and triglycerides, and increased serum levels of high-density lipoprotein-cholesterol (HDL-C), and thus improves the overall lipid profile of patients.[48]

Pitavastatin (Livalo, Sankyo/Kowa, 2003), an analog of mevastatin like rosuvastatin, has been approved for the treatment of dyslipidemia in Japan.[49]

Daptomycin (**20**, Cubicin, Cubist, 2003) is a cyclic lipopeptide antibacterial agent derived from *Streptomyces roseosporus*, which has been approved for the treatment of complicated skin and skin structure infections (cSSSIs). Daptomycin binds to bacterial cell membranes and then disrupts the membrane potential, leading to blocking of the synthesis of proteins, DNA, and RNA.[50]

Amrubicin hydrochloride (**21**, Cased, Sumitomo Pharmaceuticals Co, 2002, Japan) is a completely synthetic 9-aminoanthracycline and converts to its active form in the body.[51] Amrubicin, a derivative of doxorubicin isolated from *Streptomyces peucetius* var *caesius*, demonstrated activity comparable to that of doxorubicin on transplantable animal tumors, including P388 leukemia, sarcoma 180, and Lewis lung carcinoma, and more potent antitumor activity against human tumor xenografts of breast, lung, and gastric cancer.[52]

Biapenem (**22**, Omegacin, Wyeth Lederle Japan, 2002, Japan) is a new analog of carbapenem based on thienamycin, isolated from *Streptomyces cattleya*, an antibacterial agent effective against both Gram-negative and Gram-positive bacteria including species producing β-lactamases. Biapenem is more stable to hydrolysis by human renal dehydropeptidase-I than imipenem, meropenem, and panipenem. The early carbapenems (eg, imipenem) are not stable to hydrolysis by human renal dihydropeptidase-I (DHP-I) and consequently are coadministered with a DHP-I inhibitor (eg, cilastatin). Biapenem can be administered as a single agent without a DHP-I inhibitor.[53]

Cefditoren pivoxil (**23**, Spectracef, TAP, 2001) is an oral prodrug of cefditoren, a derivative of cephalosporin isolated from *Cephalosporium* species, and is rapidly hydrolyzed by intestinal esterases to the microbiologically active form. Cefditoren has a broad spectrum of activity against both Gram-positive and Gram-negative bacteria, and is stable to hydrolysis in the presence of a variety of β-lactamases. This drug was approved in 2001 for acute bacterial exacerbation of chronic bronchitis (AECB), group A beta-hemolytic streptococcal pharyngotonsillitis, and uncomplicated skin/skin structure infections in adult and adolescent patients.[54]

Caspofungin acetate (**24**, Cancidas, Merck, 2001) is a semisynthetic lipopeptide derived from pneumocandin B_0,

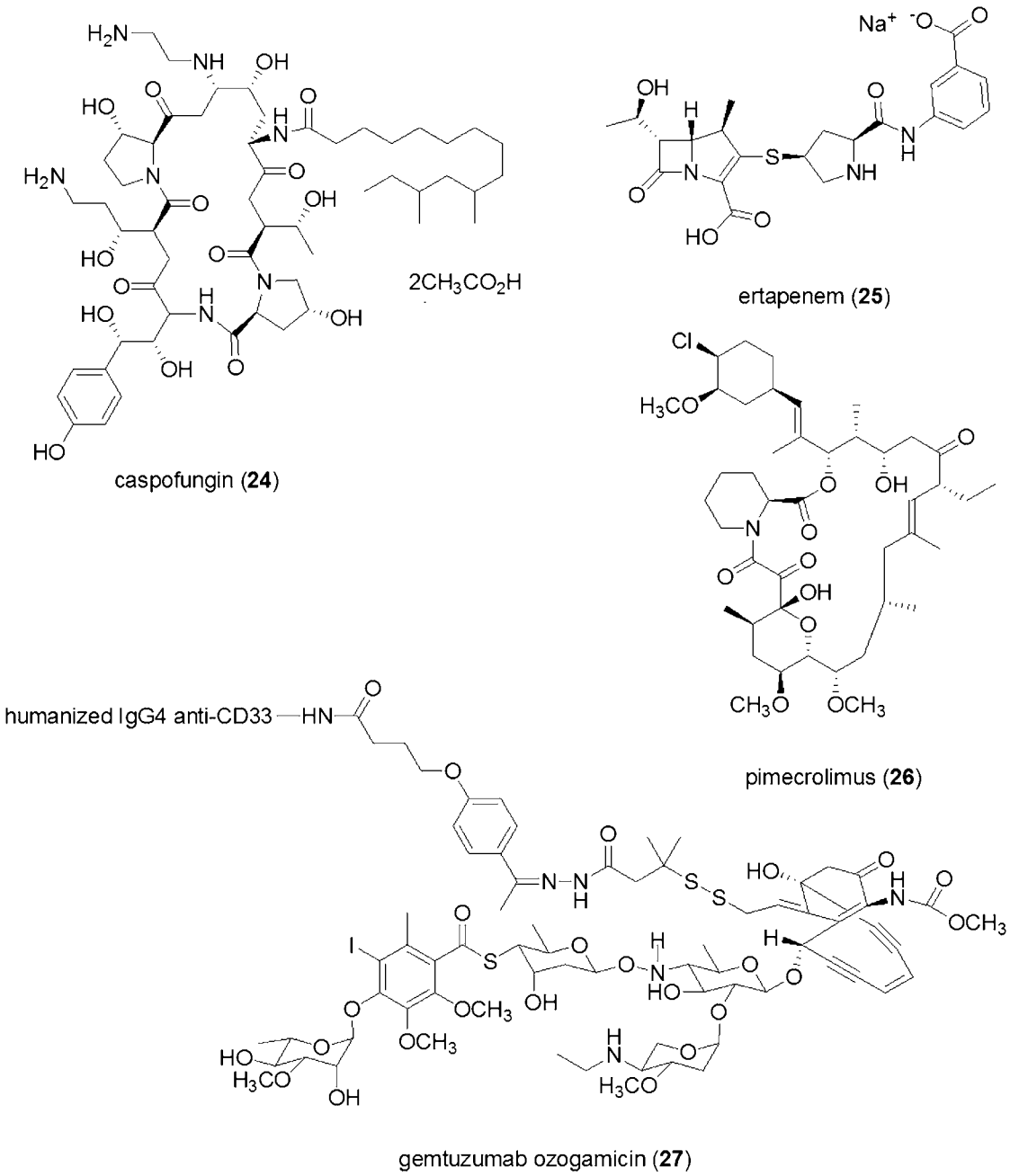

Figure 5. New drugs from terrestrial microorganisms (2000 to 2005).

a fermentation product of *Glarea lozoyensis*. It inhibits the synthesis of the glucose homopolymer β-(1,3)-D-glucan, which is an essential component of the cell wall of many fungi but is absent in mammals. The noncompetitive inhibition of β-(1,3)-D-glucan synthase by caspofungin interferes with fungal cell wall synthesis, leading to osmotic instability and death of the fungal cell.[55-57]

Ertapenem (**25**, Invanz, Merck, 2001) is a new 1β-methylcarbapenem based on thienamycin, isolated from *Streptomyces cattleya*, with broad-spectrum antibacterial activity and improved stability to hydrolysis by renal dehydropeptidase enzymes located in the brush border of the kidneys.[58] Ertapenem exhibits excellent antibacterial activity against clinically relevant Enterobacteriaceae including *Escherichia coli*, *Klebsiella* species, *Citrobacter* species, *Enterobacter* species, *Morganella morganii*, *Proteus* species, and *Serratia marcescens*.[58]

Pimecrolimus (**26**, Elidel, Novartis, 2001) is a novel analog of ascomycin, isolated as a fermentation product of *Streptomyces hygroscopicus* var *ascomyceticus*. Its mechanism of action involves blocking T cell activation via the pimecrolimus-macrophilin complex that prevents the dephosphorylation of the cytoplasmic component of the nuclear factor of activated T cells (NF-AT). This drug was approved for the treatment of inflammatory skin diseases such as allergic contact dermatitis and atopic dermatitis.[59]

Gemtuzumab ozogamicin (**27**, Mylotarg, Wyeth-Ayerst, 2000) is a prodrug of calicheamicin bound to anti-CD33 monoclonal antibody. The calicheamicins (also known as the LL-E3328 antibiotics) were discovered from fermentation products produced by *Micromonospora echinospora* ssp. *calichensis*. Lysosomes in the cells cleave the covalent link between the monoclonal antibody and calicheamicin, allowing calicheamicin release. Calicheamicin is a hydrophobic member of the enediyne family of DNA-cleaving antibiotics and effective in treatment of patients with acute myeloid lymphoma.[60,61]

Examples of Terrestrial Microbial and Fungal-derived Compounds in Clinical Trials

As potential anticancer lead compounds from microorganisms, twenty-four substances with new chemical skeletons are undergoing clinical studies (Figures 6 and 7).[12] Elsamitrucin (**28**, elsamicin A), which has a common chromophore with chartreusin from *Streptomyces chartreusis*, was isolated from the unidentified actinomycete strain J907–21. This compound binds to DNA but also inhibits activity of topoisomerase II, leading to an antitumor effect.[62,63] Brostallicin (**29**), an α-bromoacryloyl derivative of distamycin A that was isolated from the culture mycelium of *Streptomyces distallicus*, is a DNA minor groove binding anticancer agent.[64,65] Its mechanism of action is associated with activation after binding to glutathione (GSH), catalyzed by glutathione-*S*-transferase (GST), and the relatively high GST/GSH levels of cancer cells have made them more susceptible to the antitumor effects of brostallicin than normal cells.[66] Geldanamycin, a polyketide natural product, was originally obtained from *Streptomyces hygroscopicus*,[67,68] and its analogs [17-AAG (**30**) and 17-DMAG (**31**)] are currently under clinical evaluation due to their inhibition of the protein chaperone heat shock protein (HSP) 90.[69,70]

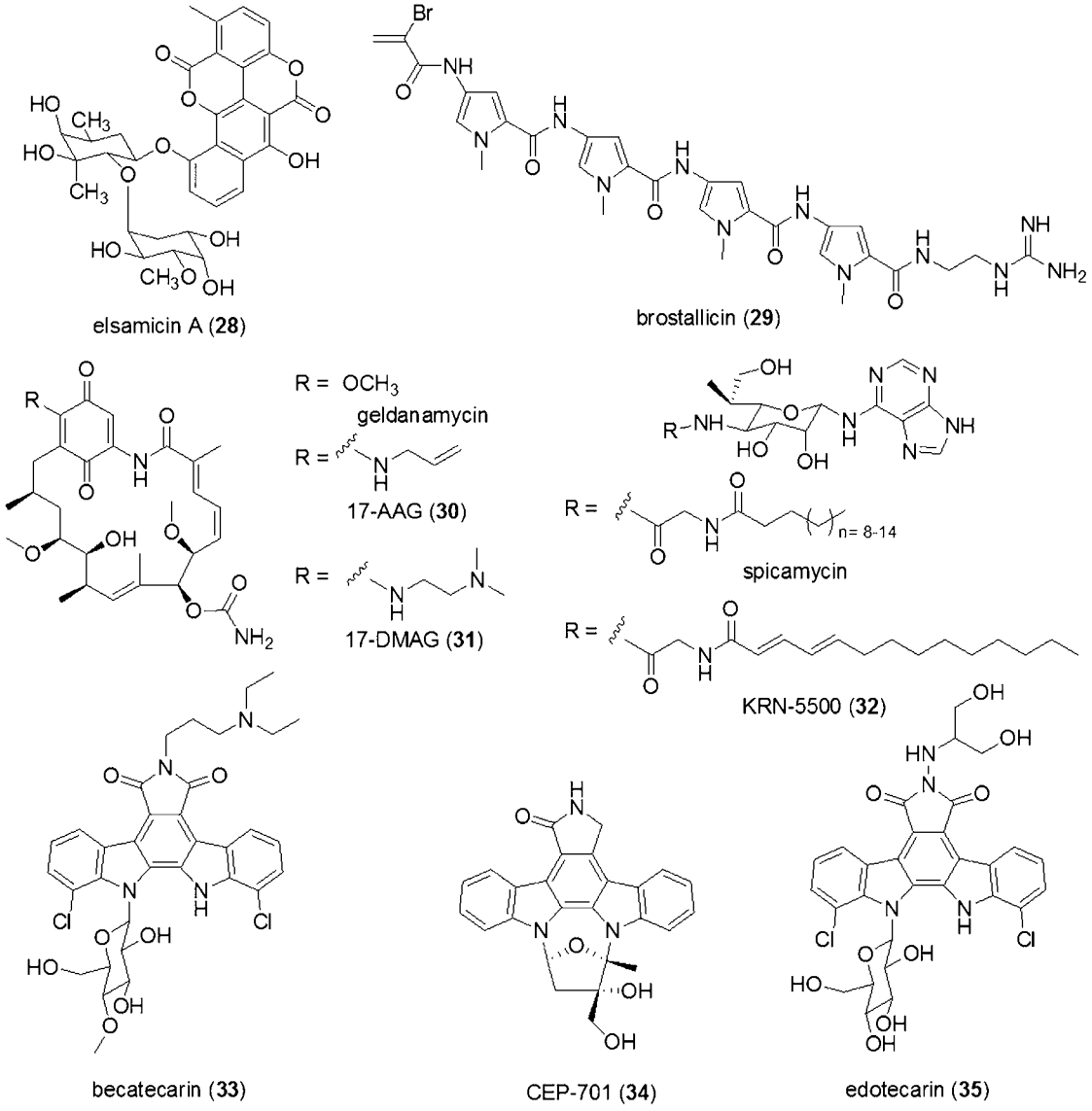

Figure 6. Terrestrial microorganism-derived drug candidates.

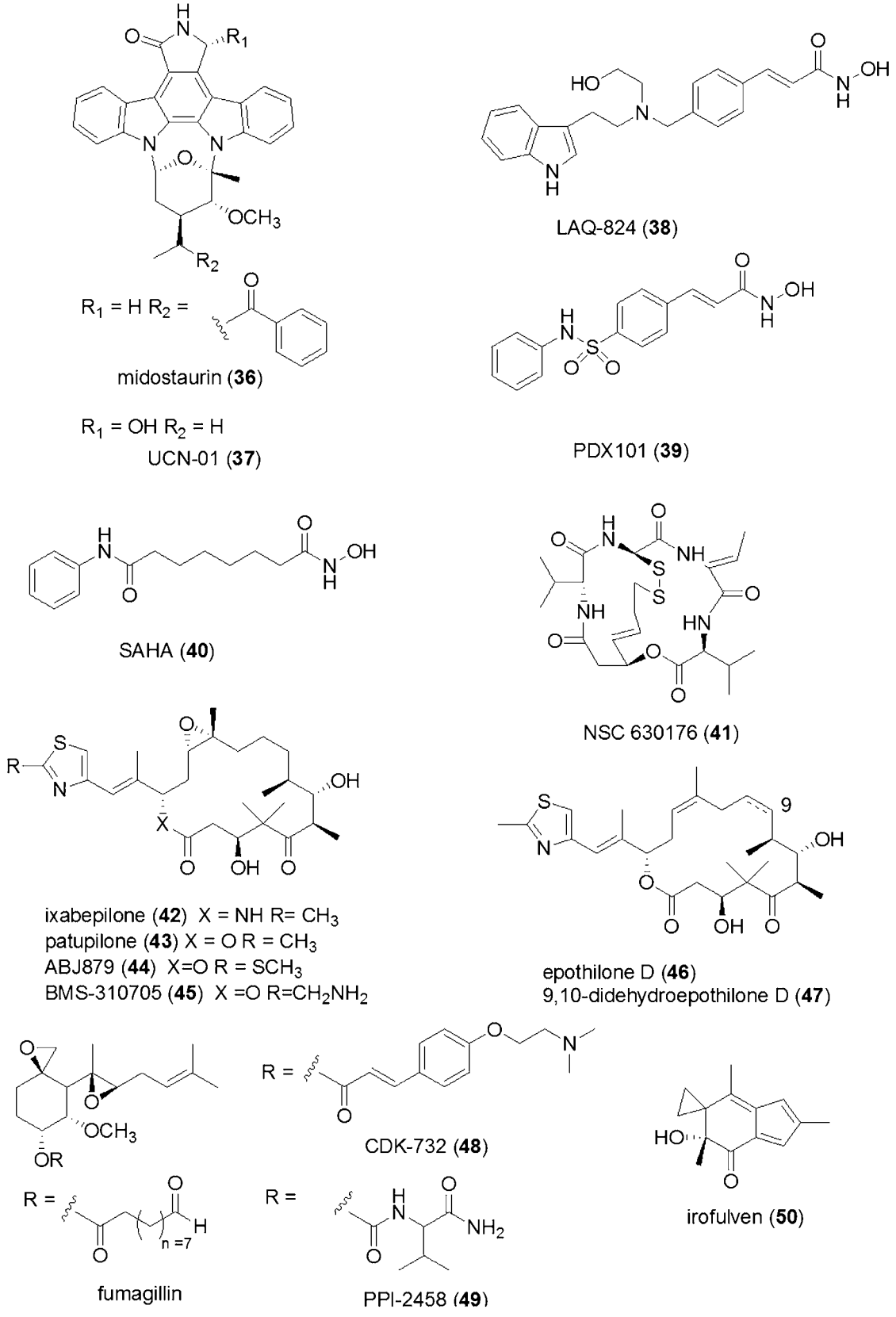

Figure 7. Terrestrial microorganism-derived drug candidates.

The spicamycins are a mixture of nucleoside-like antibiotics with an antitumor effect from *Streptomyces alanosinicus*, and an analog, KRN5500 (**32**), was reported to exhibit antitumor activity via inhibition of protein synthesis rather than the synthesis of DNA or RNA even though the mechanism of antiproliferative effect has not been established unequivocally.[71] Becatecarin (**33**), CEP-701 (**34**), edotecarin (**35**), midostaurin (**36**), and UCN01 (**37**), derivatives of staurosporine originally

found in *Nocardiopsis* species, are being developed as anticancer drugs.[72-78] Their mechanism of action is known to involve inhibition of toposiomerase I or II, FLT3 (class III tyrosine kinase), and CDK1 (cyclin-dependent kinase I). Trichostatin, a metabolite of *Streptomyces hygroscopicus*,[79] and its analogs [LAQ-824 (**38**), PDX101 (**39**), and SAHA (**40**)] have demonstrated cytotoxicity against cancer cells and rely on inhibition of histone deacetylase (HDAC), causing growth arrest, differentiation, and apoptosis of tumor cells.[80-83] The depsipeptide (NSC 630176, **41**) from *Chromobacterium violaceum*, a bicyclic peptide containing a non-cysteine disulfide bond, is structurally distinct from other known HDAC inhibitors, and is currently in phase II clinical trials for the treatment of patients with peripheral or cutaneous T cell lymphoma. The antitumor effects of this compound are correlated with the expression of angiogenesis factors, such as vascular endothelial growth factor and basic fibroblast growth factor.[84,85] The epothilones, cytotoxic macrolides discovered from the myxobacterium *Sorangium cellulosum*, were identified as microtubule-stabilizing drugs, acting in a similar manner to the taxanes. Five analogs [ixabepilone (**42**), patupilone (**43**), ABJ879 (**44**), BMS-310705 (**45**), and ZK-EPO (structure apparently not available in the public domain)] of epothilone B, epothilone D (**46**), and 9,10-didehydroepothilone D (**47**) are now undergoing investigation as candidate anticancer drugs, and their preclinical studies have indicated a broad spectrum of antitumor activity including multidrug-resistant models.[12,86-89] Fumagillin, a natural antibiotic produced by *Aspergillus fumigatus fresenius*, along with its analogs, has been shown to exert its inhibitory activity against methionine aminopeptidase 2 (MetAP2).[90] CKD-732 (**48**) and PPI-2458 (**49**), derivatives of fumagillin, inhibited tumor growth and their mechanisms of action were correlated to the level of MetAP-2 inhibition. They have also shown in vivo anti-angiogenic efficacy, inhibiting the growth of cancers in animal models.[90,91] Illudin-S is a sesquiterpenoid from *Omphalotus illudens* (known as the Jack O' Lantern mushroom) with bioluminescent properties. Its analog, irofulven (**50**), has demonstrated efficacy against several tumors in preclinical and clinical trials through induction of DNA damage, activation of MAP kinase, and apoptosis.[92-94]

Drug Discovery From Marine Organisms

Unlike the long-standing historical medical uses of terrestrial plants, marine organisms have a shorter history of utilization in the treatment and/or prevention of human disease. Among the first bioactive compounds from marine sources, spongouridine and spongothymidine from the Caribbean sponge (*Cryptotheca crypta*), were isolated serendipitously in the early 1950s.[95] They were approved as an anticancer drug (cytosine arabinoside, Ara-C) and an antiviral drug (adenine arabinoside, Ara-A), respectively, 15 years later.[96] The secondary metabolites of marine organisms have been studied extensively over the past 30 years, since a small number of academic chemists began to isolate and elucidate novel compounds from marine sources in the 1970's. Drug discovery research from marine organisms has been accelerating and now involves interdisciplinary research including biochemistry, biology, ecology, organic chemistry, and pharmacology.[97,98] Recently, much attention has been given to marine organisms due to their considerable biodiversity that has been found in the widespread oceans that cover over 70% of the world.[99] Structurally unique secondary metabolites have been isolated and identified from marine organisms and, consequently, a compound based on new chemical template has been developed and launched in 2004, while numerous other candidates are in clinical trials (Figures 8 and 9).[12,95,96]

Approved Drug

Ziconotide (**51**, Prialt, Elan, 2004), one of the ω-conotoxins, which were identified from cone snail (*Conus magus*) venom, and are 24–27 residue peptides members of the cyclic cysteine knot family. Ziconotide, known as ω-contotoxin MVIIA, selectively blocks the N-type voltage-gated calcium channel. As a novel non-opioid analgesic, ziconotide was developed for the treatment of severe chronic pain, and is currently used in pain management.[100]

Examples of Marine Organism-derived Compounds in Clinical Trials

Aplidine (**52**), an analog of the didemnins isolated from the Mediterranean tunicate, *Aplidium albicans*, has shown activity against certain tumor types (medullary thyroid carcinoma, renal carcinoma, melanoma, and tumors of neuroendocrine origin).[101] It has also been reported to inhibit the secretion of vascular endothelial growth factor (VEGF) related to angiogenesis and to arrest the cell cycle at the G_1 and G_2 phases.[101] Agelasphins, new glycosphingolipids, were isolated as antitumor agents from an Okinawan sponge, *Agelas mauritianus*.[102] Of their synthetic derivatives, KRN7000 (**53**) was selected as a candidate for clinical trials. The antitumor effect of KRN7000 has been attributed to natural killer cell activation by functioning as a ligand of VαT cell antigen receptor.[103] Bryostatin I (**54**) was isolated from the bryozoan, *Bulgula neritina*, and acts by binding to the same receptors as the phorbol esters, which were found to be tumor promoters, but bryostatin I has no tumor-promoting activity. The binding of bryostatin I to its receptors downregulates protein kinase C isoforms in various tumor cells, leading to inhibition of growth, alteration of differentiation, and/or cell death.[96,104] Discodermolide (**55**), isolated from the marine sponge, *Discodermia dissoluta*,[105] is a microtubule-stabilizing drug. This compound inhibits

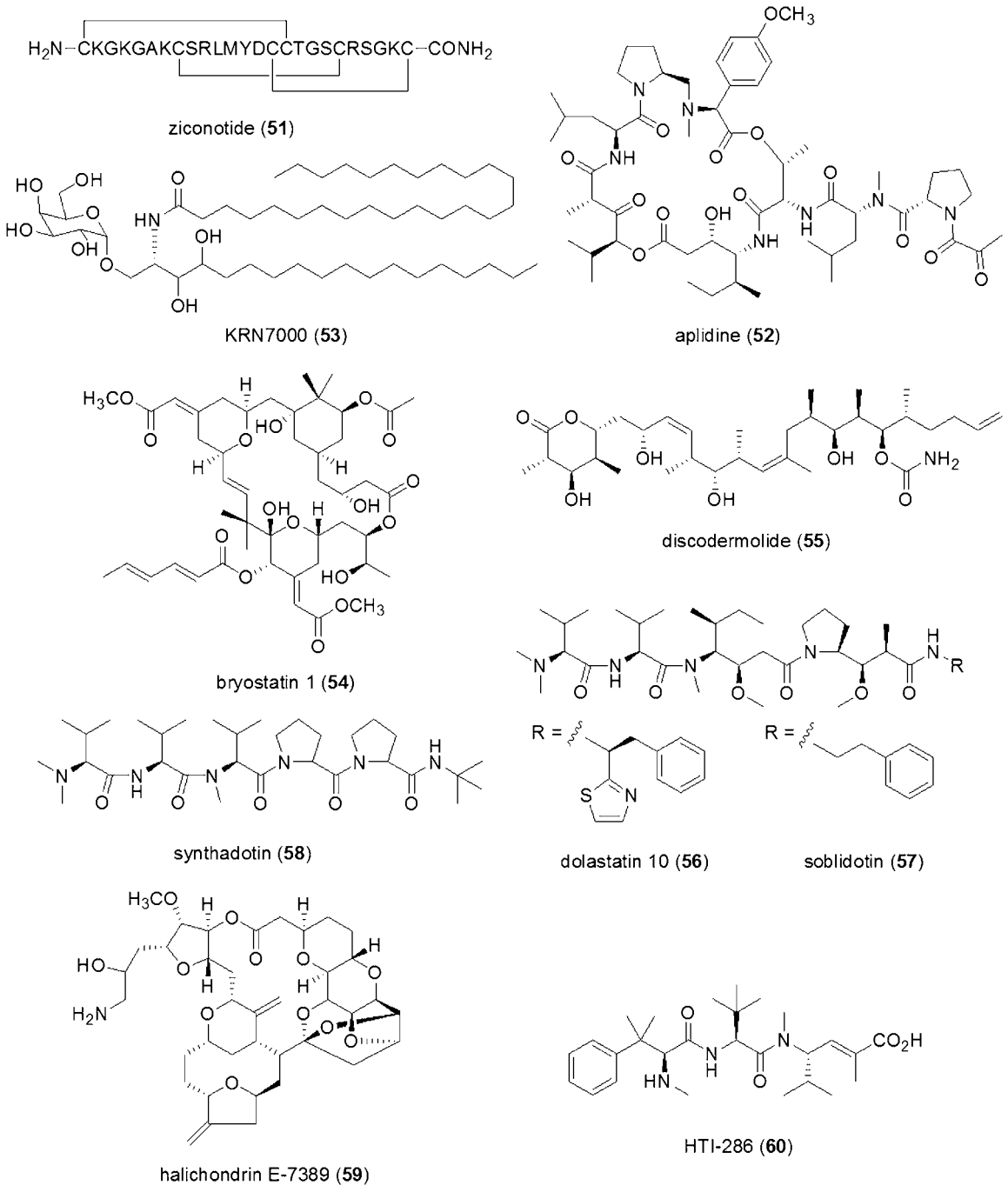

Figure 8. Marine organism-derived new drug **51** (2000 to 2005) and drug candidates **52-60**.

tumor cell growth in vitro, including against paclitaxel-and epothilone-resistant cells, and is also active in hollow fiber and xenograft mouse models.[97,98] Dolastatins 10 and 15, linear peptides isolated from the Indian Ocean sea hare *Dolabela auricularia*,[106,107] demonstrate antineoplastic activity through inhibition of microtubule assembly. Dolastatin 10 (**56**), soblidotin (**57**, a derivative of dolastatin 10), and synthadotin (**58**, an analog of dolastatin 15), are currently undergoing clinical trials.[108-111] Halichondrin E7389 (**59**), a derivative of the *Halichondria okadai* constituent, halichondrin B,[96] was found to inhibit tumor cell proliferation in association with the G_2/M arrest and microtubule polymerization.[112] HTI-286 (**60**), a synthetic analog of the tripeptide, hemiasterlin, originally isolated from the South African sponge *Hemiasterella minor*, depolymerizes microtubules and blocks cell growth. HTI-286 has also shown antitumor activity in human tumor xenograft murine models.[96,113] The cyclic depsipeptide, kahalalide F (**61**), isolated from the mollusk, *Elysia rufescens*, shows antitumor activity in patients with hepatoma, melanoma, and breast and pancreatic carcinomas. This compound did not affect bone marrow progenitors and was less sensitive to non-tumor cell

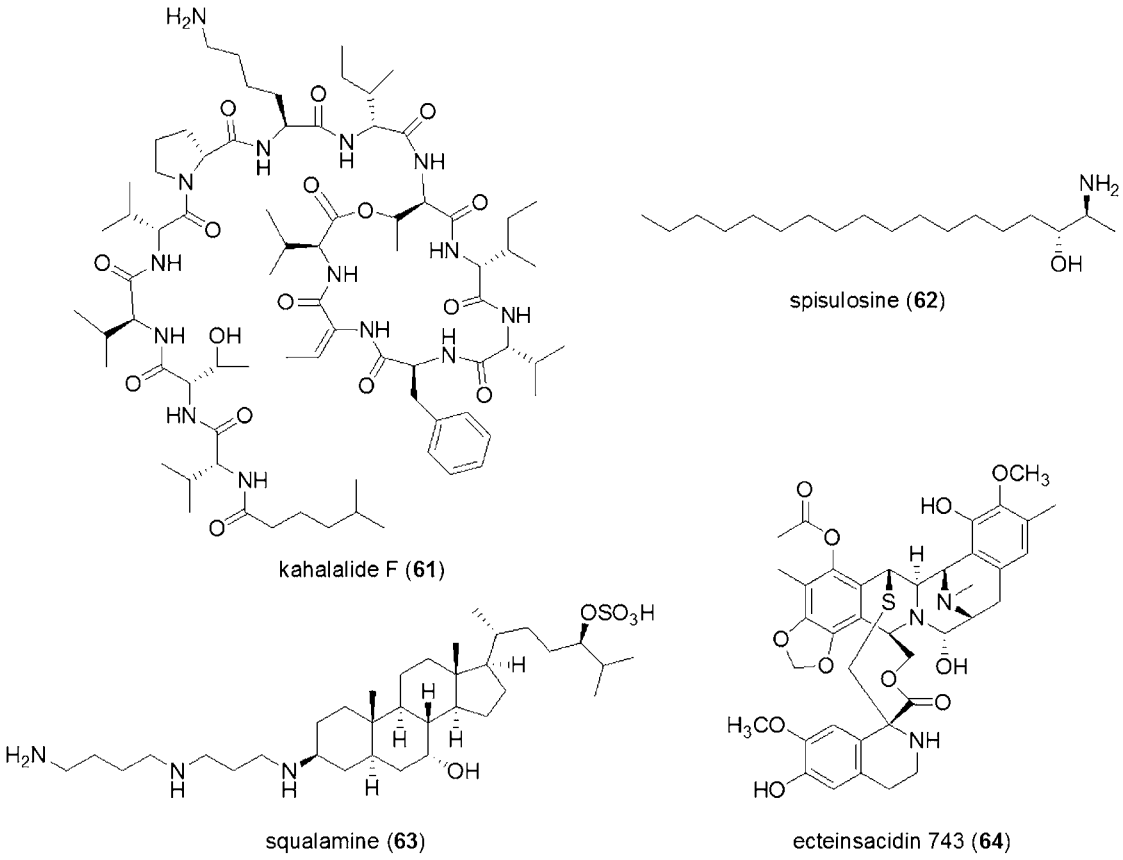

Figure 9. Marine organism-derived drug candidates.

lines.[114,115] Spisulosine (**62**), isolated from *Spisula polynyma*, has demonstrated antiproliferative activity against various human cancer cell lines (colon, gastric, pancreas, pharynx, and renal tumors), and inhibits tumor growth of human renal tumors, melanoma and prostate tumors in in vivo mouse studies.[116,117] Squalamine (**63**), an aminosterol purified from the dogfish shark, *Squalus acanthias*, is an inhibitor of growth factor-mediated endothelial cell proliferation and migration and angiogenesis.[118,119] Ecteinascidin 743 (**64**), a potent antitumor agent, was isolated from the marine tunicate *Ecteinascidia turbinata*.[120,121] Ecteinascidin 743 possesses potent cytotoxic activity against a variety of tumor cell lines in vitro and against several rodent tumors and human tumor xenografts in vivo.[121] It showed particularly high activity against advanced sarcomas that had relapsed or were resistant to conventional therapy.[122]

Drug Discovery From Terrestrial Vertebrates and Invertebrates

During the course of research on human physiology and pathology, many biochemical molecules have been discovered and their functions have been investigated. Since these biochemical compounds are related to biological action in the human body, an excess or deficiency of them has often caused pathological problems in humans. Neurohormones (adrenaline, levodopa, and histamine), peptide hormones (insulin and glucagons), sex hormones (estrogens, progesterone, and testosterone), other hormones (hydrocortisone and aldosterone), and prostaglandins (prostaglandin E_1 and E_2) are examples of compounds used for the treatment of diseases related to their physiological action.[37] Besides human biochemicals and their analogs, other drugs in this category have been discovered from various terrestrial vertebrates

L-His-Gly-L-Glu-Gly-L-Thr-L-Phe-L-Thr-L-Ser-L-Asp-L-Leu-L-Ser-L-Lys-L-Gln-L-Met-L-Glu-L-Glu-L-Glu-L-Ala-L-Val-L-Arg-L-Leu-L-Phe-L-Ile-L-Glu-L-Trp-L-Leu-L-Lys-L-Asn-Gly-Gly-L-Pro-L-Ser-L-Ser-Gly-L-Ala-L-Pro-L-Pro-L-Pro-L-Ser–NH_2

exenatide (**65**)

D-Phe-L-Pro-L-Arg-L-Pro-Gly-Gly-Gly-Gly-L-Asn-Gly-L-Asp-L-Phe-L-Glu-L-Glu-L-Ile-L-Pro-L-Glu-L-Glu-L-Tyr-L-Leu

bivalirudin (**66**)

Figure 10. New drugs from terrestrial vertebrates and invertebrates (2000 to 2005).

and invertebrates, including an inhibitor of angiotensin-converting enzyme (ACE) developed from teprotide, which was isolated from the venom of Brazilian viper (*Bothrops jararaca*) after the venom was found to cause a sudden and massive drop in blood pressure.[12] Two drugs from vertebrates and invertebrates have been approved from 2000 to the present (Figure 10).

Approved Drugs

Exenatide (**65**, Byetta, Amylin and Eli Lilly, 2005) is a synthetic analog of exenadin-4, which was originally isolated as a 39 amino acid peptide from the saliva of the Gila monster (*Heloderma suspectum*), and the first insulin mimetic found to improve glycemic control. Subcutaneous exenatide was launched in the United States for use in patients with type 2 diabetes who have failed in glycemic control by treatment with metformin and/or a sulfonylurea.[123,124]

Bivalirudin (**66**, Angiomax, MDCO, 2000) is a leech antiplatelet protein that is an inhibitor of collagen-induced platelet aggregation.[125] This compound is a new, genetically engineered form of hirudin, the substance in the saliva of the leech (*Haementeria officinalis*) and stops blood clotting. Bivalirudin is used to reduce the risk of blood clotting in adults with severe chest pain (unstable angina) who are undergoing a procedure to open blocked arteries in the heart.[126]

CONCLUSION

As shown above, 23 new drugs derived from natural sources have been launched on the market during 2000–2005, even though many pharmaceutical companies have discontinued their programs of drug discovery from natural sources. These new drugs have been approved for the treatment of cancer, neurological diseases, infectious diseases, cardiovascular and metabolic diseases, immunological, inflammatory and related diseases, and genetic disorders, which encompass many of the common human diseases. Besides new drugs launched on the market from 2000 to the present, there are a variety of new chemical entities from natural sources undergoing clinical trials. Further research on these compounds at industrial, governmental, and academic institutions is seen as vital for the enhancement of human health.

REFERENCES

1. Newman DJ, Cragg GM, Snader KM. The influence of natural products upon drug discovery. *Nat Prod Rep*. 2000;17:215-234.

2. Newman DJ, Cragg GM, Snader KM. Natural products as sources of new drugs over the period 1981-2002. *J Nat Prod*. 2003;66:1022-1037.

3. Koehn FE, Carter GT. The evolving role of natural products in drug discovery. *Nat Rev Drug Discov*. 2005;4:206-220.

4. Paterson I, Anderson EA. The renaissance of natural products as drug candidates. *Science*. 2005;310:451-453.

5. Balunas MJ, Kinghorn AD. Drug discovery from medicinal plants. *Life Sci*. 2005;78:431-441.

6. Jones WP, Chin Y-W, Kinghorn AD. The role of pharmacognosy in modern medicine and pharmacy. *Curr Drug Targets*. 2006;7:247-264.

7. Drahl C, Cravatt BF, Sorensen EJ. Protein-reactive natural products. *Angew Chem Int Ed Engl*. 2005;44:5788-5809.

8. Grifo F, Newman D, Fairfield A, Bhattacharya B, Grupenhoff J. The origins of prescription drugs. In: Grifo F, Rosenthal J, eds. *Biodiversity and Human Health.* Washington, DC: Island Press; 1997:131-163.

9. Butler MS. The role of natural product chemistry in drug discovery. *J Nat Prod*. 2004;67:2141-2153.

10. Thayer A. Bristol-Myers to settle suits. *Chem Eng News*. 2003;81:6.

11. Oberlies NH, Kroll DJ. Camptothecin and taxol: historic achievements in natural products research. *J Nat Prod*. 2004;67:129-135.

12. Butler MS. Natural products to drugs: natural products derived compounds in clinical trials. *Nat Prod Rep*. 2005;22:162-195.

13. Dewick PM. *Medicinal Natural Products: A Biosynthetic Approach.* 2nd ed. Chichester, UK: John Wiley & Sons; 2002.

14. Fabricant DS, Farnsworth NR. The value of plants used in traditional medicine for drug discovery. *Environ Health Perspect*. 2001;109:69-75.

15. Kinghorn AD. The discovery of drugs from higher plants. In: Gullo VP, ed. *The Discovery of Natural Products with Therapeutic Potential.* Boston, MA: Butterworth-Heinemann; 1994:81-108.

16. Deleu D, Hanssens Y, Northway MG. Subcutaneous apomorphine: an evidence-based review of its use in Parkinson's disease. *Drugs Aging*. 2004;21:687-709.

17. Koumis T, Samuel S. Tiotropium bromide: a new long-acting bronchodilator for the treatment of chronic obstructive pulmonary disease. *Clin Ther*. 2005;27:377-392.

18. Hall MG, Wilks MF, Provan WM, Eksborg S, Lumholtz B. Pharmacokinetics and pharmacodynamics of NTBC [2-(2-nitro-4-fluoromethyl-benzoyl)-1,3-cyclohexanedione] and mesotrione, inhibitors of 4-hydroxyphenyl pyruvate dioxygenase (HPPD) following a single dose to healthy male volunteers. *Br J Clin Pharmacol*. 2001;52:169-177.

19. Mitchell G, Bartlett DW, Fraser TEM, et al. Mesotrione: a new selective herbicide for use in maize. *Pest Manag Sci*. 2001;57:120-128.

20. Howes M-JR, Perry NSL, Houghton PJ. Plants with traditional uses and activities, relevant to the management of Alzheimer's disease and other cognitive disorders. *Phytother Res*. 2003;17:1-18.

21. Heinrich M, Teoh HL. Galanthamine from snowdrop—the development of a modern drug against Alzheimer's disease from local Caucasian knowledge. *J Ethnopharmacol*. 2004;92:147-162.

22. van Agtmael MA, Eggelte TA, van Boxtel CJ. Artemisinin drugs in the treatment of malaria: from medicinal herb to registered medication. *Trends Pharmacol Sci*. 1999;20:199-205.

23. Cirla A, Mann J. Combrestatins: from natural products to drug discovery. *Nat Prod Rep*. 2003;20:558-564.

24. Pinney KG, Jelinek C, Edvardsen K, Chaplin DJ, Pettit GR. The discovery and development of the combrestatins. In: Cragg GM, Kingston DGI, Newman DJ, eds. *Anticancer Agents from Natural Products.* Boca Raton, FL: CRC Press; 2005:23-46.

25. West CML, Price P. Combrestatin A4 phosphate. *Anticancer Drugs*. 2004;15:179-187.

26. Young SL, Chaplin DJ. Combrestatin A4 phosphate: background and current clinical status. *Expert Opin Investig Drugs*. 2004;13:1171-1182.

27. Powell RG, Weisleder D, Smith CR, Rohwedder WK. Structures of harringtonine, isoharringtonine, and homoharringtonine. *Tetrahedron Lett*. 1970;11:815-818.

28. Kantarjian HM, Talpaz M, Santini V, Murgo A, Cheson B, O'Brian SM. Homoharringtonine: history, current research, and future direction. *Cancer*. 2001;92:1591-1603.

29. Kedei N, Lundberg DJ, Toth A, Welburn P, Garfield SH, Blumberg PM. Characterization of the interaction of ingenol 3-angelate with protein kinase C. *Cancer Res*. 2004;64:3243-3255.

30. Ogbourne SM, Suhrbier A, Jones B, et al. Antitumor activity of ingenol 3-angelate: plasma membrane and mitochondrial disruption and necrotic cell death. *Cancer Res*. 2004;64:2833-2839.

31. Kamsteeg M, Rutherford T, Sapi E, et al. Phenoxodiol - an isoflavone analog - induces apoptosis in chemoresitant ovarian cancer cells. *Oncogene*. 2003;22:2611-2620.

32. Constantinou AI, Mehta R, Husband A. Phenoxodiol, a novel isoflavone derivative, inhibits dimethylbenz[*a*]anthracene (DMBA)-induced mammary carcinogenesis in female Sprague-Dawley rats. *Eur J Cancer*. 2003;39:1012-1018.

33. Shibata S, Tanaka O, Sado M, Tsushima S. The genuine sapogenin of ginseng. *Tetrahedron Lett*. 1963;4:795-800.

34. Jia W, Yan H, Bu X, Liu G, Zhao Y. Aglycone protopanaxadiol, a ginseng saponin, inhibits P-glycoprotein and sensitizes chemotherapy drugs on multidrug resistant cancer cells. *J Clin Oncol*. 2004;22:9663.

35. Kiviharju TM, Lecane PS, Sellers RG, Peehl DM. Antiproliferative and proapoptotic of triptolide (PG490), a natural product entering clinical trials, on primary cultures of human prostatic epithelial cells. *Clin Cancer Res*. 2002;8:2666-2674.

36. Fidler JM, Li K, Chung C, et al. PG490-88, a derivative of triptolide, causes tumor regression and sensitizes tumors to chemotherapy. *Mol Cancer Ther*. 2003;2:855-862.

37. Sneader W. *Drug Discovery: A History.* Hoboken, NJ: John Wiley & Sons; 2005.

38. Jarvis B, Figgitt DP, Scott LJ. Micafungin. *Drugs*. 2004;64:969-982.

39. Frattarelli DAC, Reed MD, Giacoia GP, Aranda JV. Antifungals in systemic neonatal candidiasis. *Drugs*. 2004;64:949-968.

40. Zhanel GG, Homenuik K, Nichol K, et al. The glycylcyclines: a comparative review with the tetracyclines. *Drugs*. 2004;64:63-88.

41. Chapman TM, Perry CM. Everolimus. *Drugs*. 2004;64:861-872.

42. Zhanel GG, Walters M, Noreddin A, et al. The ketolides: a critical review. *Drugs*. 2002;62:1771-1804.

43. Pastores GM, Barnett NL, Kolodny EH. An open-label, noncomparative study of miglustat in type I Gaucher disease: efficacy and tolerability over 24 months of treatment. *Clin Ther*. 2005;27: 1215-1227.

44. Weinreb NJ, Barranger JA, Charrow J, Grabowski GA, Mankin HJ, Mistry P. Guidance on the use of miglustat for treating patients with type 1 Gaucher disease. *Am J Hematol*. 2005;80:223-229.

45. Bardsley-Elliot A, Noble S, Foster RH. Mycophenolate mofetil: a review of its use in the management of solid organ transplantation. *BioDrugs*. 1999;12:363-410.

46. Curran MP, Keating GM. Mycophenolate sodium delayed release: prevention of renal transplant rejection. *Drugs*. 2005;65: 799-805.

47. Carswell CI, Plosker GL, Jarvis B. Rosuvastatin. *Drugs*. 2002;62:2075-2085.

48. Scott LJ, Curran MP, Figgitt DP. Rosuvastatin: a review of its use in the management of dyslipidemia. *Am J Cardiovasc Drugs*. 2004;4:117-138.

49. Mukhtar RYA, Reid J, Reckless JPD. Pitavastatin. *Int J Clin Pract*. 2005;59:239-252.

50. Fenton C, Keating GM, Curran MP. Daptomycin. *Drugs*. 2004;64:445-455.

51. Ogawa M. Novel anticancer drugs in Japan. *J Cancer Res Clin Oncol*. 1999;125:134-140.

52. Sugiura T, Ariyoshi Y, Negoro S, et al. Phase I/II study of amrubicin, a novel 9-aminoanthracycline, in patients with advanced non-small-cell lung cancer. *Invest New Drugs*. 2005;23:331-337.

53. Perry CM, Ibbotson T. Biapenem. *Drugs*. 2002;62:2221-2234.

54. Darkes MJM, Plosker GL. Cefditoren pivoxil. *Drugs*. 2002;62:319-336.

55. Keating G, Figgitt D. Caspofungin: a review of its use in oesophageal candidiasis, invasive candidiasis and invasive aspergillosis. *Drugs*. 2003;63:2235-2263.

56. Letscher-Bru V, Herbrecht R. Caspofungin: the first representative of a new antifungal class. *J Antimicrob Chemother*. 2003;51:513-521.

57. McCormack PL, Perry CM. Caspofungin A: review of its use in the treatment of fungal infections. *Drugs*. 2005;65:2049-2068.

58. Sader HS, Gales AC. Emerging strategies in infectious diseases: new carbapenem and trinem antibacterial agents. *Drugs*. 2001;61:553-564.

59. Gupta AK, Chow M. Pimecrolimus: a review. *J Eur Acad Dermatol Venereol*. 2003;17:493-503.

60. Lee MD, Dunne TS, Siegel MM, Chang CC, Morton GO, Borders DB. Calichemicins, a novel family of antitumor antibiotics. 1. Chemistry and partial structure of calichemicin γ_1. *J Am Chem Soc*. 1987;109:3464-3466.

61. Giles F, Estey E, O'Brien S. Gemtuzumab ozogamicin in the treatment of acute myeloid leukemia. *Cancer*. 2003;98:2095-2104.

62. Portugal J. Chartreusin, elsamicin A and related anti-cancer antibiotics. *Curr Med Chem Anticancer Agents*. 2003;3:411-420.

63. Lam KS, Veitch JA, Forenza S, Combs CM, Colson KL. Biosynthesis of elsamicin A, a novel antitumor antibiotic. *J Nat Prod*. 1989;52:1015-1021.

64. DiMarco A, Gaetani M, Orezzi P, Scotti T, Arcamone FF. Experimental studies on distamycin A – a new antibiotic with cytotoxic activity. *Cancer Chemother Rep*. 1962;18:15-19.

65. Broggini M, Marchini S, Fontana E, Moneta D, Fowst C, Geroni C. Brostacillin: a new concept in minor groove DNA binder development. *Anticancer Drugs*. 2004;15:1-6.

66. Geroni C, Marchini S, Cozzi P, et al. Brostalicin, a novel anticancer agent whose activity is enhanced upon binding to glutathione. *Cancer Res*. 2002;62:2332-2336.

67. DeBoer C, Meulman PA, Wnuk RJ, Peterson DH. Geldanamycin, a new antibiotic. *J Antibiot (Tokyo)*. 1970;23:442-447.

68. Sasaki K, Rinehart KL Jr, Slomp G, Grostic MF, Olson BC. Geldanamycin. I. Structure assignment. *J Am Chem Soc*. 1970;92:7591-7593.

69. Bisht KS, Bradbury M, Mattson D, et al. Geldanamycin and 17-allylamino-17-demethoxygeldanamycin potentiate the *in vitro* and *in vivo* radiation response of cervical tumor cells via the heat shock protein 90-mediated intracellular signaling and cytotoxicity. *Cancer Res*. 2003;63:8984-8995.

70. Kaur G, Belotti D, Burger AM, et al. Antiangiogenic properties of 17-(dimethylaminoethylamino)-17-demethoxygeldanamycin: an orally bioavailable heat shock protein 90 modulator. *Clin Cancer Res*. 2004;10:4813-4821.

71. Supko JG, Eder JP, Ryan DP, et al. Phase I clinical trial and pharmacokinetic study of the spicamycin analog KRN500 administered as a 1-hour intravenous infusion for five consecutive days to patients with refractory solid tumors. *Clin Cancer Res*. 2003;9:5178-5186.

72. Yoshinari T, Ohkubo M, Fukasawa K, et al. Mode of action of a new indolocarbazole anticancer agent, J-107088, targeting topoisomerase I. *Cancer Res*. 1999;59:4271-4275.

73. Zaugg K, Rocha S, Resch H, et al. Differential p53-dependent mechanism of radiosensitization *in vitro* and *in vivo* by the protein kinase C-specific inhibitor PKC412. *Cancer Res*. 2001;61:732-738.

74. Long BH, Rose WC, Vyas DM, Matson JA, Forenza S. Discovery of antitumor indolocarbazoles: rebeccamycin, NSC 655649, and fluoroindolocarbazoles. *Curr Med Chem Anticancer Agents*. 2002;2:255-266.

75. Chen J, De Angelo DJ, Kutok JL, et al. PKC412 inhibits the zinc finger 198-fibroblast growth factor receptor 1 fusion tyrosine kinase and is active in treatment of stem cell myeloproliferative disorder. *Proc Natl Acad Sci USA*. 2004;101:14479-14484.

76. Kondapaka SB, Zarnowski M, Yver DR, Sausville EA, Cushman SW. 7-Hydroxystaurosporine (UCN-01) inhibition of Akt Thr^{308} but not Ser^{473} phosphorylation: a basis for decreased insulin-stimulated glucose transport. *Clin Cancer Res*. 2004;10:7192-7198.

77. Smith BD, Levis M, Beran M, et al. Single-agent CEP-701, a novel FLT3 inhibitor, shows biological and clinical activity in patients with relapsed or refractory acute myeloid leukemia. *Blood*. 2004;103:3669-3676.

78. Marshall JL, Kindler H, Deeken J, et al. Phase I trial of orally administered CEP-701, a novel neurotrophin receptor-linked tyrosine kinase inhibitor. *Invest New Drugs*. 2005;23:31-37.

79. Tsuji N, Kobayashi M, Nagashima K, Wakisaka Y, Koizumi K. A new antifungal antibiotic, trichostatin. *J Antibiot (Tokyo)*. 1976;29:1-6.

80. Plumb JA, Finn PW, Williams RJ, et al. Pharmacodynamic response and inhibition of growth of human tumor xenografts by the novel histone deacetylase inhibitor PXD101. *Mol Cancer Ther*. 2003;2:721-728.

81. Arts J, Schepper S, Emelen K. Histone deacetylase inhibitors: from chromatin remodeling to experimental cancer therapeutics. *Curr Med Chem*. 2003;10:2343-2350.

82. Atadja P, Gao L, Kwon P, et al. Selective growth inhibition of tumor cells by a novel histone deacetylase inhibitor, NVP-LAQ824. *Cancer Res*. 2004;64:689-695.

83. Monneret C. Histone deacetylase inhibitors. *Eur J Med Chem*. 2005;40:1-13.

84. Sandor V, Bakke S, Robey RW, et al. Phase I trial of the histone deacetylase inhibitor, depsipetide (FR901228, NSC 630176), in patients with refractory neoplasms. *Clin Cancer Res*. 2002;8:718-728.

85. Shiraga T, Tozuka Z, Ishimura R, Kawamura A, Kagawama A. Identification of cytochrome P450 enzymes involved in the metabolism of FK228, a potent histone deacetylase inhibitor, in human liver microsomes. *Biol Pharm Bull*. 2005;28:124-129.

86. Kosmidis PA, Manegold C. Advanced NSCLC: new cytostatic agents. *Lung Cancer*. 2003;41:S123-S132.

87. Starks CM, Zhou Y, Liu F, Licari PJ. Isolation and characterization of new epothilone analogues from recombinant *Myxococcus xanthus* fermentation. *J Nat Prod*. 2003;66:1313-1317.

88. Goodin S, Kane MP, Rubin EH. Epothilones: mechanism of action and biologic activity. *J Clin Oncol*. 2004;22:2015-2025.

89. Rizvi N, Villalona-Calere M, Lynch T, et al. Phase II study of KOS-862 (epothilone D) as second-line therapy in non-small cell lung cancer. *Lung Cancer*. 2005;49:S266-S267.

90. Chun E, Han CK, Yoon JH, Sim TB, Kim Y-K, Lee K-Y. Novel inhibitors targeted to methionine aminopeptidase 2 (MetAP2) strongly inhibit the growth of cancers in xenografted nude model. *Int J Cancer*. 2005;114:124-130.

91. Bernier SG, Lazarus DD, Clark E, et al. A methionine aminopeptidase-2 inhibitor, PPI-2458, for the treatment of rheumatoid arthritis. *Proc Natl Acad Sci USA*. 2004;101:10768-10773.

92. McMorris TC, Anchel M. Fungal metabolites. The structures of the novel sesquiterpenoids illudin-S and -M. *J Am Chem Soc*. 1965;87:1594-1600.

93. McMorris TC, Kelner MJ, Wang W, Yu J, Estes LA, Taetle R. (Hydroxymethyl)acylfulvene: an illudin derivative with superior antitumor properties. *J Nat Prod*. 1996;59:896-899.

94. Wang J, Wiltshire T, Wang Y, et al. ATM-dependent CHK2 activation induced by anticancer agent, irfulven. *J Biol Chem*. 2004;279:39584-39592.

95. Newman DJ, Cragg GM. Advanced preclinical and clinical trials of natural products and related compounds from marine sources. *Curr Med Chem*. 2004;11:1693-1713.

96. Newman DJ, Cragg GM. Marine natural products and related compounds in clinical and advanced preclinical trials. *J Nat Prod*. 2004;67:1216-1238.

97. Capon RJ. Marine bioprospecting-trawling for treasure and pleasure. *Eur J Org Chem*. 2001;2001:633-645.

98. Haefner B. Drugs from the deep: marine natural products as drug candidates. *Drug Discov Today*. 2003;8:536-544.

99. Jensen PR, Fenical W. Marine microorganisms and drug discovery: current status and future potential. In: Fusetani N, ed. *Drugs from the Sea.* New York: Karger; 2000:6-29.

100. Schroeder CI, Smythe ML, Lewis RJ. Development of small molecules that mimic the binding of ω-conotoxins at the N-type voltage-gated calcium channel. *Mol Divers*. 2004;8:127-134.

101. Taraboletti G, Poli M, Dossi R, et al. Antiangiogenic activity of aplidine, a new agent of marine origin. *Br J Cancer*. 2004;90:2418-2424.

102. Natori T, Morita M, Akimoto K, Koezuka Y. Agelasphins, novel antitumor and immunostimulatory cerebrosides from the marine sponge *Agelas mauritianus. Tetrahedron*. 1994;50:2771-2784.

103. Hayakawa Y, Rovero S, Forni G, Smyth MJ. α-Galactosylceramide (KRN7000) suppression of chemical- and oncogene-dependent carcinogenesis. *Proc Natl Acad Sci USA*. 2003;100:9464-9469.

104. Newman DJ. The bryostatins. In: Cragg GM, Kingston DGI, Newman DJ, eds. *Anticancer Agents from Natural Products.* Boca Raton, FL: CRC Press; 2005:137-150.

105. Honore S, Kamath K, Braguer D, Wilson L, Briand C, Jordan MA. Suppression of microtubule dynamics by discodermolide by a novel mechanism is associated with mitotic arrest and inhibition of tumor cell proliferation. *Mol Cancer Ther*. 2003;2:1303-1311.

106. Pettit GR, Kamano Y, Herald CL, et al. The isolation and structure of a remarkable marine animal antineoplastic constituent: dolastatin 10. *J Am Chem Soc*. 1987;109:6883-6885.

107. Pettit GR, Kamano Y, Dufresne C, Cerny RL, Herald CL, Schmidt JM. Isolation and structure of the cytostatic linear depsipeptide dolastatin 15. *J Am Chem Soc*. 1989;54:6005-6006.

108. Kerbrat P, Dieras V, Pavlidis N, Ravaud A, Wanders J, Fumoleau P. Phase II study LU103793 (dolastatin analogue) in patients with metastatic breast cancer. *Eur J Cancer*. 2003;39:317-320.

109. Marks RS, Graham DL, Sloan JA, et al. A phase II study of the dolastatin 15 analogue LU 103793 in the treatment of advanced non-small-cell lung cancer. *Am J Clin Oncol*. 2003;26:336-337.

110. Kindler HL, Tothy PK, Wolff R, et al. Phase II trials of dolastatin-10 in advanced pancreaticobiliary cancers. *Invest New Drugs*. 2005;23:489-493.

111. Perez EA, Hillman DW, Fishkin PA, et al. Phase II trial of dolastatin-10 in patients with advanced breast cancer. *Invest New Drugs*. 2005;23:257-261.

112. Jordan MA, Kamath K, Manna T, et al. The primary antimiotic mechanism of action of the synthetic halichondrin E7389 is suppression of microtubule growth. *Mol Cancer Ther*. 2005;4:1086-1095.

113. Loganzo F, Hari M, Annable T, et al. Cells resistant to HT-286 do not overexpress P-glycoprotein but have reduced drug accumulation and a point mutation in α-tubulin. *Mol Cancer Ther*. 2004;3:1319-1327.

114. Suárez Y, González L, Cuadrado A, Berciano M, Lafarga M, Muñoz A. Kahalalide F, a new marine-derived compound, induces oncosis in human prostate and breast cancer cells. *Mol Cancer Ther*. 2003;2:863-872.

115. Janmaat ML, Rodriguez JA, Jimeno J, Kruyt FAE, Giaccone G. Kahalalide F induces necrosis-like cell death that involves depletion of ErB3 and inhibition of Akt signaling. *Mol Pharmacol*. 2005;68:502-510.

116. Jimeno JM, Garcia-Gravalos D, Avila J, Smith B, Grant W, Faircloth GT. ES-285, a marine natural product with activity against solid tumors. *Clin Cancer Res*. 1999;5:3792s.

117. Cuadros R, Garcini EM, Wandosell F, Faircloth G, Fernández-Sousa JM, Avila J. The marine compound spisulosine, an inhibitor of cell proliferation, promotes the disassembly of actin stress fibers. *Cancer Lett*. 2000;152:23-29.

118. Moore KS, Wehrli S, Roger H, et al. Squalamine: an aminosterol antibiotic from the shark. *Proc Natl Acad Sci USA*. 1993;90:1354-1358.

119. Hao D, Hammond LA, Eckhardt SG, et al. A phase I and pharmacokinetic study of squalamine, an aminosterol angiogenesis inhibitor. *Clin Cancer Res*. 2003;9:2465-2471.

120. Soares DG, Poletto NP, Bonatto D, Salvador M, Schwartsmann G, Henriques JAP. Low cytotoxicity of ecteinascidin 743 in yeast lacking the major endonucleolytic enzymes of base and nucleotide excision repair pathways. *Biochem Pharmacol*. 2005;70:59-69.

121. Rinehart KL. Antitumor compounds from tunicates. *Med Res Rev*. 2000;20:1-27.

122. Chen X, Chen J, De Paolis M, Zhu J. Synthetic studies toward ecteinascidin 743. *J Org Chem*. 2005;70:4397-4408.

123. Malhotra R, Singh L, Eng J, Raufman J-P. Exendin-4, a new peptide from *Heloderma suspectum* venom, potentiates cholecystokinin-induced amylase release from rat pancreatic acini. *Regul Pept*. 1992;41:149-156.

124. Keating GM. Exenatide. *Drugs*. 2005;65:1681-1692.

125. Gladwell TD. Bivalirudin: A direct thrombin inhibitor. *Clin Ther*. 2002;24:38-58.

126. Ledizet M, Harrison LM, Koskia RA, Cappello M. Discovery and pre-clinical development of antithrombotics from hematophagous invertebrates. *Curr Med Chem Cardiovasc Hematol Agents*. 2005;3:1-10.